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09/888,049	06/21/2001	Kevin P. Francis	PXE-013.US; 9400-0013	6970

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EXAMINER

LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/888,049	Applicant(s) FRANCIS ET AL.	
	Examiner David A. Lambertson	Art Unit 1636	

-- Th **MAILING DATE** of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-59 is/are pending in the application.
- 4a) Of the above claim(s) 43,44 and 53-57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-42,45-52,58 and 59 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 6) ☐ Other: _____

DETAILED ACTION***Election/Restrictions***

Applicant's election with traverse of Group I (claims 1-42, 45-52, and 58-59) filed September 2, 2003 is acknowledged. The traversal is on the ground(s) that: (a) a search of all groups would not be burdensome because a search of one group would be *likely* to find art related to all of the groups, (b) failure to search all of the groups would be unduly burdensome of the Office and (c) failure to search all of the groups would be financially burdensome to Applicant. This is not found persuasive because of the following reasons: (a) a search of the prior art would not necessary yield art on all of the groups, and this is implicit in the fact that a search of one group would only *likely* (and not definitely) find art on all of the groups, therefore the searches must be commensurate in scope in order to not be burdensome; (b) the burden on the Office is not an issue for rejoinder of restricted groups, especially when the restriction is clearly and properly set forth by the Office; (c) financial burden to the Applicant, while regrettable, is also not an acceptable reason to rejoin properly restricted groups. Furthermore, the restriction as set forth in the previous Office Action properly set forth that the different inventions were classified in different classes and subclasses, which is all that need be shown in order to justify a restriction.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-59 are pending in the instant application. Claims 43, 44 and 53-57 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-42, 45-52, 58 and 59 are ready for examination in the instant application.

Priority

Applicant's claim for domestic priority to US Applications 60/216,257 and 60/274,105 under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statements filed on October 16, 2001, February 14, 2002 and February 26, 2002 have been considered, and a signed and initialed copy of each form PTO-1449 is attached to this Office Action. It is noted that two references are crossed through as having not been considered. The first, FR 2,693,475 is a foreign language document, for which no translation has been received; as such, it is impossible to discern the teachings held within. The second document, reference AE-2 as indicated on the IDS filed February 26, 2002, is merely a duplication of a reference that has been indicated as considered in a previous IDS.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See specifically page 36, lines 7-8.

Claim Objections

Claim 46 is objected to because of the following informalities: claim 46 is dependent upon a claim that is withdrawn from consideration as being drawn to a non-

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elected invention. The claim is withdrawn from consideration until such time as the dependency is changed. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-42, 45-52, 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claims 1 and 21 recite the limitation “derived from” a transposon. This limitation is indefinite because it is unclear what steps constitute the derivation of the transposon sequence or how much derivation (i.e., mutation) of the sequence is required for the transposon to be considered “derived.”

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 13, 23 and 47-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Knudtson *et al.* (*Gene* **137**: 217-222, 1993; see entire document; henceforth Knudtson).

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Knudtson teaches the construction of a transposon cassette derived from the TN4001 transposon, where the transposon contains a promoterless *lacZ* reporter/marker gene (see for example the Abstract and Figure 1), as well as a vector comprising the transposon cassette, a bacterial origin of replication and the ampicillin resistance gene (see for example Figures 2 and 3). Importantly, the TN4001 transposon was originally isolated from the Gram-positive bacteria *Staphylococcus aureus* and was known to contain the gentamycin antibiotic resistance gene and imperfect internal repeat sequences within the IS256 arm of the transposon (see for example page 217-218, the bridging paragraph, and Figures 2 and 3). Knudtson teaches the use of the transposon cassette for the identification of promoter sequences in the Gram-positive bacteria *Mycobacterium*. Specifically, the transposon cassette is transformed into the host cell where it integrates into the genome, thereby modifying the cell, and expression of the marker/reporter gene is mediated by a promoter sequence contained within the host genome (see for example the Abstract and pages 221-222). In order for the assay to be functional, the transposon cassette must necessarily encode a transposase under the regulation of a promoter sequence that is active in the targeted host cell (otherwise, there would be no integration of the transposon cassette into the host genome).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4-5, 14-15, 50-52 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudtson as applied to claim 1 (and claims 2, 3, 13, 23 and 47-49, as well) under 35 USC § 102(b), in view of Lajoie *et al.* (US Patent No. 6,110,661; see entire document; henceforth Lajoie).

Knudtson teaches all of the elements as set forth under 35 USC § 102(b). However, Knudtson does not teach using a luciferase gene as the marker/reporter gene in the transposon cassette.

Lajoie teaches the construction of transposon cassette containing a promoterless lux (luciferase gene) reporter gene (such as *luxC*, *luxD*, *luxA*, *luxB* and *luxE*; see for example Figure 7), where the cassette can be used to modify a host cell chromosome by integration (see for example column 6, lines 35-45). Thus, this cassette is used in effectively the same manner as the cassette described by Knudtson. Lajoie further teaches that other reporters would be useful and effective within the transposon, giving specific examples of the *lacZ* gene, other lux genes, or green fluorescent protein (GFP). However, Lajoie makes it clear that the lux genes are the reporters of choice because, among other things, they give the most rapid response times (see for example column 6, lines 50-60).

It would have been obvious to modify the transposon cassette of Knudtson by substituting the promoterless lux gene taught by Lajoie for the *lacZ* gene taught by Knudtson because both references teach the use of transposons containing marker/reporter genes for integration into the genomes of host cells, and Lajoie clearly indicates the interchangeability of the *lacZ* and lux genes. The ordinary skilled artisan

would have been motivated to combine the teachings in order to use the most preferred reporter gene, which Lajoie teaches are the *lux* genes. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when practicing the combined teachings because it simply involves the substitution of one marker genes (*lacZ*) for another (*lux*) which is describes in one of the references (Lajoie) as being preferable.

Claims 6-10 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudtson in view of Lajoie as applied above to claim 4 (and claims 5, 14, 15, 50-52 and 58) under 35 USC § 103(a), and in further view of Jacobs (IDS reference AO-1 of the October 26, 2001 filed IDS; see entire documents; henceforth Jacobs).

Knudtson in view of Lajoie teaches all of the elements set forth above in the rejection of claim 4 under 35 USC 103(a). However, Knudtson in view of Lajoie does not specifically teach the use of a ribosome binding sequence (RBS) from a Gram-positive bacterium in front of the marker/reporter genes.

Jacobs teaches the employment of the *xynB* RBS to translationally couple the expression of the *luxA* and *luxB* genes in Gram-positive bacteria (see for example page 252-253, the bridging paragraph). Jacobs further teaches that this use of a strong RBS in front of the *lux* genes can provide a general means of getting high levels of expression of in vivo bioluminescence in Gram-positive bacteria (see for example page 225, last paragraph), where the expression of the *lux* genes had provided a considerable problem (see for example page 251, bottom of the first paragraph, left column). In other words, Jacobs provides a general solution to remedy a long-standing problem associated with the

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expression of lux genes in Gram-positive bacteria, which is an important tool for biochemistry (see for example page 251, paragraph bridging the left and right columns).

It would have been obvious to modify the transposon cassette of Knudtson in view of Lajoie by inserting the ribosome binding sequence taught by Jacobs in front of the lux reporter genes because each teaching involves the expression of lux genes in Gram-positive bacteria, therefore the teachings are related to a common process and clearly combinable. The ordinary skilled artisan would have been motivated to combine the teachings in order to resolve a long-standing problem in the art, the poor expression of lux genes in Gram-positive bacteria (as taught by Jacobs); the teachings of Jacobs provide a significant resolution to this problem by employing the use of an RBS from a Gram-positive organism in front of the lux genes, thus the skilled artisan would want to employ this strategy in front of any lux gene in any reporter construct to be used in Gram-positive bacteria in order to enhance the expression (and therefore detection) of the reporter gene. Absent evidence to the contrary, the skilled artisan would have had a reasonable expectation of success when practicing the claimed invention because the teachings both relate to a common property, the expression of lux genes in Gram-positive bacteria.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudtson in view of Lajoie in further view of Jacobs as applied above to claim 7 (and claims 6, 8-10 and 16) under 35 USC § 103(a), and in further view of Baldwin *et al.* (*Biochem.* **29**: 5509-5515, 1990; see entire document; henceforth Baldwin).

Knudtson in view of Lajoie in further view of Jacobs teaches all of the elements set forth in the rejection under 35 USC § 103(a). However, this teaching does not provide for the use of the *luxY* gene, specifically, in the reporter construct described by the combined teachings. To briefly reiterate the key point, Lajoie specifically teaches that a *lux* gene and the *lacZ* gene are interchangeable as reporter genes.

Baldwin teaches the identification of a yellow fluorescent protein, *luxY* (see for example the Abstract).

It would have been obvious to modify the transposon cassette of Knudtson in view of Lajoie in further view of Jacobs by substituting the *luxY* reporter gene taught by Baldwin for any of the other *lux* reporter genes because Lajoie provides the suggestion that any *lux* gene can be substituted for the *lacZ* reporter gene, and the *luxY* gene is a *lux* gene. The ordinary skilled artisan would have been motivated to combine the teachings of Knudtson in view of Lajoie in further view of Jacobs with those of Baldwin in order to make use of all possible reporter genes in their reporter constructs. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when practicing the combined teachings because the crux of the combination is a simple substitution of one reporter gene for another, and it is suggested in the teachings by Lajoie that any *lux* gene can be a useful reporter gene, and that the *lux* and *lacZ* genes equivalently interchangeable.

Claims 17, 18 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knudtson in view of Lajoie in further view of Jacobs as applied to claims 4, 15 and

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16 (as well as claims 5, 14, 50-52 and 58) under 35 USC § 103(a), and in further view of Wagner *et al.* (US Patent No. 5,591,601; see entire document; henceforth Wagener).

Knudtson in view of Lajoie in further view of Jacobs teaches all of the elements set forth in the rejection under 35 USC § 103(a). However, this teaching does not specifically teach the use of the kanamycin resistance gene (or other antibiotic resistance genes) in the transposon cassettes/vectors.

Wagner teaches that it is obvious to substitute one antibiotic resistance gene for another in a plasmid/vector of interest (see for example column 10, lines 26-32).

It would have been obvious to modify the transposon cassette taught by Knudtson in view of Lajoie in further view of Jacobs by substituting the kanamycin antibiotic resistance gene taught by Wagner for the antibiotic resistance gene taught by Knudtson because Wagner clearly indicates that the use of one antibiotic resistance gene is equivalent to the use of another (i.e., one can be functionally substituted for another). The ordinary skilled artisan would have been motivated to combine the teachings in order to increase the range of antibiotic resistance markers that can be used as selection markers for the transformation of host cells; this is of particular use when using bacterial strains that may inherently possess a resistance to a given antibiotic. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when practicing the claimed invention because the interchangeability of antibiotic markers has been used prolifically in the field of molecular biology, as evidenced by the specific teachings of Wagner.

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Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU 1636


JAMES KETTER
PRIMARY EXAMINER